146. (New) The method of claim 22, wherein the polymer is a polymer containing at least three contiguous linked lysines.

147. (New) The method of claim 22, wherein the polymer is a polymer containing at least four contiguous linked lysines.

148. (New) The method of claim 22, wherein the polymer is a polymer containing at least five contiguous linked lysines.

149. (New) The method of claim 25, wherein the polymer is a polymer containing at least five contiguous linked glutamines.

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150. (New) The method of claim 25, wherein the polymer is a polymer containing at least ten contiguous linked glutamines.

151. (New) The method of claim 25, wherein the polymer is a polymer containing at least fifteen contiguous linked glutamines.

152. (New) The method of claim 25, wherein the polymer is a polymer containing at least twenty contiguous linked glutamines.

153. (New) A composition comprising

a microparticle comprising an active agent and a polymer having transglutaminase substrate reactive groups, wherein the transglutaminase substrate reactive groups are surface available, wherein the polymer comprises a polymer of amino acids and wherein at least 20% of the amino acids are glutamines.

154. (New) The composition of claim 153, wherein the polymer comprises at least three contiguous, linked glutamines.

Remarks

Claims 21, 22, 24, 25, 102, 119, 123, 135 and 136 have been amended.

Claims 21, 24, 102, 119, 123, 125, 135 and 136 have been amended to recite that a glutamine or lysine rich polymer is one having at least 20% glutamines or lysines, or one having at least three contiguous, linked glutamines or lysines. Claim 123 has been amended to recite that the polymer contains at least three contiguous linked glutamines. A polymer having at least 20% glutamines is claimed in new claim 153 which draws support from claims 123 and 136. Support for the other amendments can be found in the specification on page 18, lines 16-21.

Applicants acknowledge the Examiner's finding that claims 22 and 25 are free of the prior art. Claims 22 and 25 have been amended to recite the limitations of the claims from which each depends (i.e., claims 1 and 18). Claims 22 and 25 should now be allowable.

New claims 145-154 have been added. Claims 145-148 are dependent from claim 22, and each individually recites elements of the Markush group of claim 22. Claims 149- 152 are dependent from claim 25, and each individually recites elements of the Markush group of claim 25. Claims 153 and 154 derive from claim 123 and 136.

If these amendments require an additional claim fee, the Examiner is authorized to charge the small entity fee to the Deposit Account of the undersigned as indicated on the transmittal.

Claims 1-26, 51, 75-77, 102, 117-119, 123-125, 135, 136, 143-154 are currently pending.

No new matter has been added.

Information Disclosure Statement and Cited References

Along with the previous response dated February 11, 2002, Applicants submitted an Information Disclosure Statement with a modified Form 1449 citing a number of references that were previously cited in the parent case having serial number 09/359,920. These references are indicated with an asterisk (*). Only the Wagner et al. reference (supplied as full article) and Lemaitre et al. reference (supplied as abstract) were provided to the Examiner as these references had not been cited in the parent case. Applicants re-submit herewith a copy of the Lemaitre abstract. If the Examiner is not able to locate the cited references in the parent application, Applicants will submit new copies.

Applicants also submitted an Information Disclosure Statement on July 18, 2002 citing the International Search Report for the corresponding PCT application, and copies of co-pending applications. Applicants request the Examiner acknowledge receipt of this latter Information Disclosure Statement.

Rejection under 35 U.S.C. §112, second paragraph

The Examiner has rejected claims 1-25, 21, 22, 24, 25, 102, 117-119, 123-125, 135 and 136 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner has rejected claims 21, 24, 102, 117-119, 123-125, 135 and 136 because of the recitation of "glutamine-rich" and "lysine-rich" renders these claims uncertain as to meaning and scope. According to the Examiner, the term "rich" is relative and subjective.

Applicants respectfully direct the Examiner to page 18, lines 16-21 which teach that

> "a polymer rich in glutamine or lysine is a molecule wherein at least 20% of the units of the polymer carry a carboxamide, an aliphatic amine, or both, such as glutamine, lysine or glutamine and lysine, or wherein the molecule includes at least 3, preferably 4 and most preferably 5 separate and discretely spaced by a regular distance carboxamides or aliphatic amines, such as occurs with contiguous, linked glutamines or lysines."

Applicants have previously argued that the teaching in the specification is sufficiently definite, that one would understand the metes and bounds of claims reciting the term "rich", particularly in view of the above passage. Notwithstanding this and in an earnest effort to expedite prosecution, Applicants have amended the claims to recite that a "glutamine-rich" polymer is one comprising at least 20% glutamines or one having at least three contiguous linked glutamines. Similarly, those claims reciting a "lysine-rich" polymer are amended to recite a polymer comprising at least 20% lysines or a polymer having at least three contiguous linked lysines.

In view of the foregoing, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims under 35 U.S.C. §112, second paragraph.

Rejection under 35 U.S.C. §102(b)

The Examiner has rejected claims 123-125, 143 and 144 under 35 U.S.C. §102(b), as being anticipated by Bernstein et al. (US 5,679,377) or Mathiowitz et al. (US 5,271,961). According to the Examiner, "the protein microspheres of Bernstein et al. or Mathiowitz et al. are inherently glutamine-rich, and inherently contain sufficient transglutaminase reactive substrate groups on their surfaces to attach the microspheres to skin in the presence of endogenous or exogenous transglutaminase as in claims 123-125." The Examiner further states that "crosslinking protein with transglutaminase as disclosed by Bernstein et al. or Mathiowitz et al. is optional and not essential ... (and) ... the microspheres of Bernstein et al. or Mathiowitz et al.

can contain a non-nucleic acid active agent and have a particle size in the range of claims 143 and 144."

Applicants respectfully traverse the rejection. A claim element may be missing from a reference yet still inherent in its teaching only if it is "necessarily present in the thing described in the reference" and would be so recognized by those of ordinary skill. An element that *may* be present according to the teaching of the reference is not inherent in the reference. (See MPEP § 2112.) There is no evidence that, after manufacture, the microspheres taught by either Bernstein et al. or Mathiowitz et al. will *necessarily* have surface available transglutaminase substrate reactive groups (i.e., accessible to and reactive with transglutaminase), or that such groups will *necessarily* be present in an amount sufficient to attach the microspheres to a skin surface in the presence of endogenous or exogenous transglutaminase. This is particularly so given that Bernstein et al. and Mathiowitz et al. teach crosslinking the protein in order to increase the stability of the microparticle, and that the protein microparticles may be formed with a (non-protein) polymer coating.

In view of the foregoing, Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. §102(b).

Rejection under 35 U.S.C. §103(a)

Rejection in view of Richardson et al., Bernstein et al., Mathiowitz et al. and Won

The Examiner has rejected claims 1, 3-19, 23, 24, 26, 51, 75-77, 123-125, 135, 136, 143 and 144 under 35 U.S.C. §103(a), as being unpatentable over Richardson et al. (U.S. 5,490,980) in view of Bernstein et al. (US 5,679,377) or Mathiowitz et al. (US 5,271,961) each taken with Won (US 5,145,675).

In order to establish a prima facie case of obviousness, there must exist a motivation or suggestion to combine references and a reasonable expectation of success, and the combination must teach or suggest each element of the pending claims. Applicants respectfully traverse the rejection because none of these requirements has been established.

The teachings of Richardson et al., Mathiowitz et al., Bernstein et al., and Won were discussed in the previously filed Response, and thus will not be re-iterated in their entirety here.

Richardson et al. stresses the criticality of alkylamines as reactive groups for transglutaminase, and therefore cannot teach modification of agents with glutamines. In addition, the reference teaches the individual addition of alkylamine groups to an active agent, and therefore cannot teach conjugation of alkylamine groups to each other (as found in a

polymer). The reference does not teach or enable attachment to skin using endogenous transglutaminase, as it explicitly teaches the need for exogenously supplied transglutaminase. It therefore cannot teach "sufficient amounts" of transglutaminase amine reactive groups for attachment to a body tissue in the presence of endogenous transglutaminase. The reference also does not teach microparticle attachment as a method for delivering active agent to skin, as the fluorescent spheres of Richardson et al. were used as markers rather than drug carriers.

Bernstein et al. and Mathiowitz et al. teach biodegradable protein microspheres preferably made from prolamines (i.e., proteins having large numbers of hydrophobic amino acids such as glutamine). These references further teach that prolamines may be treated with enzymes such as transglutaminase prior to particle formation in order to increase stability, and that the resultant particles may have a non-protein coating. Won teaches chemically and biologically inert particles that preferably have reactive groups removed in order to preserve an active agent contained therein.

There is no motivation to combine Richardson et al. with either Bernstein et al. or Mathiowitz et al. at least because Richardson et al. explicitly stresses the criticality of amine groups, and not carboxamide groups (such as those of glutamine), as the reactive substrate for transglutaminase. It is known in the art that lysine is a better substrate for transglutaminase than glutamine. Richardson et al. capitalized on this and teaches explicitly an aliphatic amine substrate of transglutaminase, not a carboxamide such as glutamine. Bernstein et al. and Mathiowitz et al. provide microparticles having large numbers of glutamines. The glutamines can be crosslinked with exogenously supplied enzymes. There is no suggestion in the references to *attach* the microparticles of Bernstein et al. or Mathiowitz et al. to skin. Nor is there any suggestion in the references to take the active component of Richardson et al. into the microparticles of Bernstein et al. or Mathiowitz et al. Won does not supply the motivation to combine the references either, at least because Won teaches away from the use of microparticles having reactive groups for the delivery of an active agent.

There similarly could be no reasonable expectation of success since Richardson et al. teaches amines as suitable substrates for exogenous transglutaminase, Bernstein et al. and Mathiowitz et al. teach glutamine containing microparticles, and Won teaches away from the use of particles that contain reactive groups for use in agent delivery.

Finally, even if such combination could be made (and Applicants maintain that it cannot), the combination still does not teach or suggest all the pending claim limitations. Specifically, the combination fails to teach microparticles having surface available transglutaminase substrate

reactive groups present in an amount sufficient to attach the microparticle to a skin surface in the presence of endogenous transglutaminase, or non-labeling microparticles having surface available transglutaminase substrate reactive groups present in an amount sufficient to attach microparticles to a skin surface in the presence of exogenous transglutaminase.

The combination of Richardson et al., Bernstein et al. or Mathiowitz et al., taken with Won, is improper for the reasons stated above. Accordingly, the Examiner has failed to establish a *prima facie* case of obviousness in view of these references.

Rejection in view of Richardson et al., Bernstein et al., Mathiowitz et al., Won and Zheng et al.

The Examiner has rejected claims 2, 20, 21, 102 and 117-119 under 35 U.S.C. §103(a) as being unpatentable over the above references and further in view of Zheng et al.

According to the Examiner, "Zheng et al. disclose producing microspheres containing lysine amino groups to covalently link the microspheres to desired molecules ... (and) ... the microspheres are a blend of a poly(lactide-co-glycolide) and poly (ε CBZ-L-lysine)." The Examiner states that "it would have been obvious to provide the protein microspheres with lysine groups by blending the protein of the microspheres with poly (ε CBZ-L-lysine) as suggested by Zheng et al. since Richardson et al. disclose reacting alkylamine groups with transglutaminase to provide attachment of an active agent to skin."

Applicants respectfully traverse the rejection for the reasons stated below.

Applicants have addressed the obviousness rejection in view of Richardson et al., and Bernstein et al. or Mathiowitz et al., either in further view of Won. The combination of these references is improper given the lack of motivation to combine such references (particularly in view of the inconsistent teachings of these references), the lack of reasonable expectation of success for such combination, and the failure of the combination to teach or suggest all of the pending claim limitations.

The Zheng et al. reference teaches microspheres having surface available lysine groups to which a variety of biologically active molecules can be attached. The in vivo properties of these microspheres can be altered based on the nature of the active agents attached to their surface.

The teachings of the Zheng et al. reference are inconsistent with those of Richardson et al. In particular, Zheng et al. teaches that reactive amines on the surface of microparticles are to be used to attach active agents or targeting molecules for delivery to specific sites in the body. Once so modified, the microparticles would no longer be a suitable substrate for transglutaminase activity as taught by Richardson et al. The Zheng et al. reference does not

contemplate that the microparticles can be directly attached to a body tissue via the reactive amine groups, and accordingly, it fails to teach that the surface reactive lysines must be present in amounts sufficient to attach the microparticle to a body tissue such as skin in the presence of endogenous or exogenous transglutaminase.

There is no motivation to combine the references at least because the references teach different purposes. Moreover, there is no reasonable expectation of success in using the microspheres of Zheng et al. in the method of Richardson et al. because the microsphere of Zheng et al. would not be transglutaminase substrates following the modification taught by Zheng et al. Finally, the combination still fails to teach the pending claim limitations at least because it does not teach microparticles having sufficient surface available transglutaminase substrate reactive groups in amounts sufficient for endogenous transglutaminase activity or exogenous transglutaminase activity (for non-labeling particles). Accordingly, the Examiner has failed to make a *prima facie* case of obviousness over the art of record.

In view of the foregoing, Applicants respectfully request that the Examiner reconsider and withdraw the rejections under 35 U.S.C. §103(a).

Rejection under the Judicially Created Doctrine of Obviousness-Type Double Patenting

The Examiner has rejected claims 1-26, 51, 75-77, 102, 117-119, 123-125, 135, 136, 143 and 144 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-48 of U.S. Patent No. 6,267,957 (Green et al.) in view of Bernstein et al. or Mathiowitz et al. and each taken with Won.

Applicants are preparing a terminal disclaimer over US 6,267,957 and will submit an executed version to the Examiner shortly.

Applicants respectfully request that the Examiner withdraw the rejection under the judicially created doctrine of obviousness-type double patenting upon receipt of the terminal disclaimer.

Summary

Applicants believe that each of the pending claims is now in condition for allowance. Applicants respectfully request that the Examiner telephone the undersigned in the event that the claims are not found to be in condition for allowance.

If the Examiner has any questions and believes that a telephone conference with Applicants' agent would prove helpful in expediting the prosecution of this application, the Examiner is urged to call the undersigned at (617) 720-3500 (extension 266).

Respectfully submitted,

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x11.07.02

APPENDIX A

MARKED-UP CLAIMS

Please amend the claims as follows:

21. (Amended) The method of claim 18, wherein the polymer [is lysine-rich at] comprises a surface available terminus having at least 20% lysines or at least three contiguous linked lysines.

22. (Twice Amended) [The] A method of [claim 18,] treating a subject to attach microparticles to a skin surface containing endogenous transglutaminase of the subject comprising

contacting the skin surface containing endogenous transglutaminase with microparticles having surface available transglutaminase substrate reactive groups in an amount sufficient to attach the microparticles to the skin surface in the presence of the endogenous transglutaminase,

allowing the microparticles to remain in contact with the skin surface for a time sufficient to permit a layer of microparticles to covalently attach to the skin surface,

wherein the transglutaminase substrate reactive groups are part of a polymer, and

wherein the polymer comprises a polymer selected from the group consisting of polymers containing:

(a) at least two contiguous linked lysines,

(b) at least three contiguous linked lysines,

(c) at least four contiguous linked lysines, and

(d) at least five contiguous linked lysines.

24. (Amended) The method of claim 18, wherein the polymer [is glutamine-rich at] comprises a surface available terminus having at least 20% glutamines or at least three contiguous linked glutamines.

25. (Twice Amended) [The] A method of [claim 18,] treating a subject to attach microparticles to a skin surface containing endogenous transglutaminase of the subject comprising

contacting the skin surface containing endogenous transglutaminase with microparticles having surface available transglutaminase substrate reactive groups in an amount sufficient to attach the microparticles to the skin surface in the presence of the endogenous transglutaminase,

allowing the microparticles to remain in contact with the skin surface for a time sufficient to permit a layer of microparticles to covalently attach to the skin surface,

wherein the transglutaminase substrate reactive groups are part of a polymer, and

wherein the polymer comprises a polymer selected from the group consisting of polymers containing:

(a) at least five contiguous linked glutamines,

(b) at least ten contiguous linked glutamines,

(c) at least fifteen contiguous linked glutamines, and

(e) at least twenty contiguous linked glutamines.

102. (Amended) A composition comprising

a microparticle comprising an active agent and a [lysine-rich] polymer having transglutaminase substrate reactive groups, wherein the microparticle is non-biodegradable, and the transglutaminase substrate reactive groups are surface available, and the polymer comprises a polymer of amino acids having at least 20% lysines or at least three contiguous linked lysines.

119. (Amended) The composition of claim 102, wherein the [lysine-rich] polymer comprises a polymer of amino acids and wherein at least 50% of the amino acids are lysine.

123. (Amended) A composition comprising

a microparticle comprising an active agent and a [glutamine-rich] polymer having transglutaminase substrate reactive groups, wherein the transglutaminase substrate reactive groups are surface available, and the polymer comprises a polymer of amino acids having at least three contiguous linked glutamines.

135. (Twice Amended) The composition of claim 123, wherein the [glutamine-rich] polymer is covalently linked to the synthetic polymer.

136. (Amended) The composition of claim 123, wherein the [glutamine-rich] polymer comprises a polymer of amino acids and wherein at least 20% of the amino acids are glutamines.